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EDITORIAL

On these pages the editor offers his opinions, unshackled by advertising patrons and unrestrained by anything save a sense of the decent and the truthful. The editor, alone, is responsible for their type, their tone and their tenor.

PRELUDE TO SLEEP

THERE is an interval between the time of going to bed and the moment of sweet soporific surrender, when the brain must somehow, somewhere, slow its pace and ease its train of thought to sleep's quiet wayside station.

Sometime it is an interval when the memory sniffs awhile at fragrant petals, fallen from rosy hours, part of the day just ended. And that is wholesome, fetching a true repose!

Othertime it may be that the mulling minutes pass by in Indian file, scowling and growling at the indiscretions of a wayward day. So are fence rails let down for nightmares to scamper in.

Then there is that undisciplined, whirligig time, when thoughts engendered by a tired brain explode like flashes from a pinwheel and fall forthwith to pyrotechnic desuetude. Sleep so reached is an obstinate sleep, sullen, slow and stupid!

But there is still another kind and quality of interval, one of a certain starkness, when night is antonymic and a strange and often unwanted clarity pierces through its black cloth, sending a sheer spectral ray shimmering through the darkness. And the playful dust of the brain, at other times invisible, casts back its manifold reflections. Surfaces of day ignored insensates are keen illumined to the mental eye and colored with new significance. Sleep stands by and waits, too often vainly waits, for great events. Fortunate is the man, whose such preludes to sleep are prolific, even though not productive of else than entertainment. For to him at last comes sleep, not as a hurt and poppied sleep, but as a contented, concentrated slumber, wrapped in sheer conceit and sure of happy outcome.

It is as if one gently, proudly stows the brain away on a pillow stuffed with hope and thrilled with the guarantee of continued cerebral promise. Such a sleep mortgages a merry tomorrow.

In the kaleidoscope of my prelude to sleep, a night or so ago, a certain conceit challenged the remembering of its episoded facets.

Here they are, to the best of a prodded memory.

There was a recalling of Judge Wilson's remarks to the indicted head of Slippery Rock Teachers' College. Said the judge, in effect: "There is ample evidence of mismanagement of the institution's affairs, but we must remember with satisfaction that, under the defendant's supervision, this institution turned out a football team last year, second to none, a feat of 'no mean credit'." And my sleep-approaching mental molecules arranged themselves in Roman fashion. *"O Tempora, O Immores!"*

Better than this facet was the fast recollection of this nation's new declaration of independence. Thus—

In this day of world-wide calamity, we are not as in 1914, deprived of necessities, manufacture monopolized by others. We are sitting pretty among nations, thanks to our scientists, and particularly to our chemists. Yet the brain-on-the-train queried why, if the chemist can make a nation selfsufficient in a war-torn world, can't he do something about removing the causes of war? President Compton of the Massachusetts Institute of Technology foresees the time when science will do just that—by producing in the laboratory the raw materials for which nations are now ready to fight. Hail the day when Peace, though chemist fabricated, again prevail and the lion and the lamb abide in easy, useful amity!!

Then a cerebral cell somehow spilled this soliloquy, clean from the Moravian Garden of Gregor Mendel, the Augustinian Abbot, and relayed by Thomas Hunt Morgan, that elephantine minded experimenter with the filmy fruit fly.

Said Morgan: "Chromosomes in the cell are always definite in number for each species of animal or plant—8 for the fruit fly, 14 for the garden or sweet pea, 42 for modern wheat, 54 for the monkey, 48 for man. Note that these are all even numbers. Could it be that the chromosomes are paired, so that half belong to the female and half to the male?"; which seems like an unfamiliar division! But that was not all. *Genes,* whatever they are, complicated the picture, once in every hundred episodes, and this seems to be the one per cent. that dominates evolution. Listen to the monstrosities that prevailed when another experimenter shot these *genes* full of X-rays.

This is what happened to them. Came flies with eyes that bulged; flies with hair that was curly, ruffled, parted, fine, coarse; flies that were bald; flies with extra legs or no legs at all; flies with wings of every conceivable shape; big flies and little flies; active flies and sluggish flies; sterile flies and fertile flies.

And thought I, now on the thin edge of sleep, "How long will it be before—

'God calls his caravan at man's approach
Calls his swift caravan, and moves—moves on!' "

Obviously precipitated by the evening's proofreading of a masterly dissertation on bio-catalysts as presented in this issue of the Journal by Dr. Ehrenstein, next came a veritable shower of drenching thoughts and cross-thoughts. Peripheral groups whirled about the nucleus of morphine; the tricyclic phenanthrene system flashed and revealed how much it has to do, not with coal tar derivatives and synthetic complexes, but with the intimacies of our physiology, the bile acids, the sterols, the sex hormones, plant hormones and plant principles; how from it, is so readily rationalized the synthesis of oestrogenic and carcinogenic substances and of morphine-like analgesics. Yet on the brink of sleep, I knew how *little* I knew, how little *anyone* knew, *yet,* of the real relations existing between the poppy alkaloid morphine, cholesterol, the gall acids, the sex hormones, catalysts of history, and the blue phenanthrene dyestuff that so cheaply colors my stockings—and now so colors my way to sleep.

So help me, if I remember aright, my thoughts next turned *"ad astra."* I recalled that Galileo had disclosed the vaster region of the unseen stars, and Herschel with his large telescopes had tremendously extended the known size of cosmic space. Hubble more recently had pushed back the horizons of the mind to include distances overwhelmingly stupendous. In 1934 he held that the most remote galaxy visible from Mt. Wilson was 300 million light-years away, but within a year he had discovered another estimated to be 500 million light-years (three sextillion miles) distant, the present outpost of observable space. Though mathematics records the round numbers, no brain lasts long enough to grasp their meaning. Nor did mine, for then "God gave me His beloved sleep"—till morning came, too soon, to tell me of the day ahead.

IVOR GRIFFITH.

IN MEMORIAM

PROFESSOR DR. ALEXANDER TSCHIRCH

PROF. Dr. Alexander Tschirch died in Bern, Switzerland, December 2, 1939. This life imbued with love and work came to an end and with sorrow and grief we bow before death that does not discriminate against the insignificant nor the great.

Alexander Tschirch was one of the truly great men in the field of Pharmacy. He completed a most brilliant career despite all the vicissitudes of life. Born in Guben (Niederlausitz, Germany), October 17th, 1856, he started his practical training as an apprentice in Loschwitz near Dresden and passed his preliminary State Board Examination in Dresden, September, 1875, with high marks, "Very good." He then worked in several places as an assistant pharmacist: in Oberlahnstein, Freiburg i. Br. and Bern. In Bern he laid the foundation for his future, since it was here that he was offered the opportunity of making many chemical and galenical preparations on a large scale. He also published here his first scientific note. He devoted his spare time to microscopy and he soon acquired a thorough knowledge in this field. A large collection of transverse and longitudinal sections of herbs and drugs was started at this time. From Bern he went to Berlin to attend the University of Berlin, where he was greatly attracted by the botanical lectures. Eichler was his great teacher. However, he was very disappointed in the lectures on Pharmacognosy which were not well presented. He graduated with high marks and at the same time got his license as a pharmacist. He completed his studies at the University of Freiburg i. Br. with a dissertation in botany and received his Ph. D. Going back to Berlin he became an assistant at the Plant Physiological Institute of the Agricultural Institute of Technology and took an active part in organizing the German Botanical Society. In 1884 Tschirch received the "Venia Legendi," an academic grade comparable to that of assistant professor. His curriculum in teaching consisted chiefly in botanical microscopical courses with special reference to official herbs and plants. His lectures dealt with Pharmacognosy. In 1890 he was called to Bern as an associate professor.

This marked the beginning of Tschirch's great career. Pharmacognosy had always played an important role in Switzerland and

during his many years in Bern he exercised a compelling influence in building up an institute and making Bern the centre of Pharmacognosy. He soon became full professor and was made director of the Pharmaceutical Institute. By his own diligent work, his outstanding teaching abilities and his great personality he elevated the Pharmacognosy from a descriptive, dead science to an experimental and live science. Among his outstanding achievements are the "Pharmacognostic Atlas," published in co-operation with Oesterle and his internationally famous "Handbuch für Pharmacognosie." His institute was surrounded by a large botanical-pharmacognostical garden and in recognition of his scientific contributions to medicine, he became professor in the medical faculty.

He celebrated his 80th birthday October 7th, 1936. Great honors were bestowed upon him. Shortly before he had published his autobiography, "Erlebtes und Erstrebtes" (What I experienced and what I strived for). Acknowledging a congratulatory letter from Berlin, he wrote:

> "I am content to see that Pharmacognosy in Germany finds more serious consideration in teaching and in research, also cultivation of medicinal herbs—two tasks which I considered my duty, which I undertook to promote. So at the end of my life, I see my dream come true, a hope which I had almost given up. It has its advantages to grow old."

Alexander Tschirch has traveled for 66 working years through the whole field of Botany and Pharmacognosy and acquired a knowledge and keen understanding for this science granted to only few persons. In his book "The Life of the Plant and Its Soul," he announces the quintessence of his perception in these words:

> "From all this we must deduce that there is one directing, guiding and acting power besides the automatically working vital force. We can call the former 'Soul'."

The soul of this great scholar ascended to still higher perceptions.

(Translated by Elsa Ehrenstein, from "Deutsche Apotheker Zeitung," Vol. 54, 99.)

ORIGINAL ARTICLES

THE HORMONES OF THE SEX GLANDS AND OF THE ADRENAL CORTEX*

By Maximilian Ehrenstein, Ph. D.
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AMONG the endocrine glands the hypophysis or pituitary gland plays a predominant role. Undoubtedly all the other endocrine glands depend more or less on the function of the hypophysis. This organ is attached to the base of the brain; its size is very small, and in man measures 6 x 8 x 14 mm. As far as the gross anatomical structure is concerned, we differentiate between the anterior lobe, the posterior lobe and the pars intermedia which connects the former two. Of these parts we know most about the hormonal function of the anterior lobe. It influences fundamentally a great many of the body's functions. Its hormones regulate growth, reproduction and metabolism. The hormones of the anterior pituitary commonly act on other endocrine glands, thereby regulating their hormonal function. The nomenclature of these pituitary hormones acting on other endocrine glands uses frequently the ending "tropic" derived from the Greek tropos: turning or acting upon. Thus we know a gonadotropic hormone acting on the gonads, or sex glands; a thyrotropic hormone acting on the thyroid, an adrenotropic hormone acting on the adrenals, and so on. Among these hormones of the anterior lobe of the pituitary we know most about the gonadotropic hormone which regulates almost the whole function of the sex glands. The production of such a hormone by the pituitary was definitely proved by Zondek and Aschheim in 1926. By the implantation of a minute particle of anterior lobe tissue from man or animals into infantile female animals they were able to initiate precocious ovarian function. It turned out that the pituitaries of either male or female individuals furnish the same gonadotropic factor and that this gonadotropic substance brings about precocious maturity in either sex. The gonadotropic factor is therefore non-specific as far as sex is concerned.

* Lecture delivered before the Philadelphia Branch of the American Pharmaceutical Association on November 14, 1939, and before the Second Annual Seminar on Modern Pharmaceutical Practice conducted by the Philadelphia College of Pharmacy and Science on January 30, 1940.

Zondek and Aschheim proved that a hormone, showing to a certain degree the physiological properties of the anterior pituitary gonadotropic substance, is present in the urine of pregnant women. The most important feature is the fact that this substance can be found in large quantities as early as a few days after conception. Apparently pregnancy results in an overproduction of this hormone and the excess is eliminated in the urine. This substance, designated "Prolan," appears to be present only in pregnancy urine of man and monkeys. The so-called Aschheim-Zondek pregnancy test is now generally known. I may mention a few details of this test. In order to explain this clearly, I shall review a few fundamental facts concerning the structure and the normal function of the female sex organs. They consist of the ovaries, the tubules (Fallopian tubes) connecting the ovaries with the uterus, the uterus and the vagina. All these organs are undeveloped and relatively small in immature animals. On the ovaries are found small prominences, the so-called Graaffian follicles. In infantile animals they are tiny and undeveloped. In adult animals one or several of these follicles will be undergoing certain changes at any given time. They grow larger and within each of them one ovum is ripening. In man usually only one follicle develops at a time. After a certain period—in man about fourteen days—the follicle bursts and the ripe ovum is released. In other words ovulation takes place. From now on the former follicle undergoes a characteristic change; a yellow mass grows in its cavity, the so-called corpus luteum. If fertilization of the ovum does not occur, the corpus luteum gradually undergoes degeneration. If pregnancy occurs, the corpus luteum is maintained throughout pregnancy. The corpus luteum is essential for the maintenance of pregnancy. Habitual abortion may be due to dysfunction of the corpus luteum. Parallel with these changes in the ovaries go certain changes in the uterus and vagina which will be explained later.

The gonadotropic factor of the anterior pituitary or that obtained from pregnancy urine is able to stimulate maturation of the Graaffian follicles, and formation of corpora lutea in immature animals. In each such experiment the animals have to be sacrificed in order to reveal the effect. The carrying out of this Aschheim-Zondek reaction, or in this country also the Friedman test, requires only four or two days respectively. As a pregnancy test its reliability amounts to about 98 per cent. Relatively little is known of the chemistry of the gonadotropic factors, except that they are related

to the proteins. It might be mentioned that gonadotropic substances can also be secured from pregnant mare's serum.

As was outlined, the gonadotropic factors are non-specific as far as sex is concerned. Hence, such a factor, obtained from either males or females, will stimulate the development of either male or female sex glands. Specific sex hormones, characteristic of each sex, are formed within the sex glands themselves. We have discussed the characteristic changes taking place in the ovaries, which are the female sex glands. Investigations have shown that the developing follicle contains a certain hormone, the follicular hormone. A second, physiologically different hormone is the corpus luteum hormone; it is found only in the corpus luteum though accompanied by the follicular hormone.

The changes which occur in the ovaries of mature women are closely connected with those which take place in the mucous membrane of the uterus, the so-called endometrium. Through the influence of the follicular hormone, produced in the ripening follicle, the uterine endometrium undergoes a characteristic growth; furthermore certain glands develop in the endometrium. This phase of the uterus is called the proliferation phase; it lasts until about the fourteenth day of the menstrual cycle. At that time the mature follicle in the ovary ruptures and thus ovulation takes place. In the cavity of the ruptured follicle the corpus luteum is developed. Two hormones, the follicular and the corpus luteum hormone, are now liberated and become effective in the organism. Under the influence of the corpus luteum hormone the uterine endometrium commences to function very actively: its glands begin to secrete. At the height of this phase, the so-called secretion phase, the endometrium is prepared for the imbedding of the fertilized ovum. If fertilization of the ovum does not occur, the uterus casts off the secreting endometrium and hemorrhage, generally called menstruation, takes place. Following menstruation, the whole cycle is started again.

It must be mentioned that in the uteri of certain animals, for instance rabbits, only the phase of proliferation usually occurs, and along with it the so-called estrous cycle of the mucous membrane of the vagina. If coitus does not occur, the proliferated endometrium of the uterus degenerates and the cycle starts anew. If coitus does take place while the animal is at the height of estrus, however, ovulation occurs and the phase of secretion begins in the uterus and

thus provision is made for the implantation of the fertilized ovum. The estrous cycle in rabbits is therefore analogous only to the first half of the menstrual cycle in man, which is under the influence of the follicular hormone. When a rodent is at the height of the estrous cycle, in other words, when it is in heat, the mucous membrane of the vagina discharges characteristic, cornified, squamous cells.

The procedure for measuring the follicular hormone is the Allen (Edgar)-Doisy test. Castrated rats or mice cannot get into estrus because of the lack of the ovaries. Artificial administration of follicular hormone will bring about the estrous reaction of the vaginal mucosa. Vaginal smears can easily be examined under the microscope. Follicular hormone and other substances, capable of bringing about this reaction, are called estrogenic substances. A mouse unit, for instance, is defined as the quantity which just suffices to produce the estrous response in the castrated mouse.

The test method for the measuring of the physiological activity of the corpus luteum hormone which is mainly used in this country was worked out by Corner and Allen (Willard). The hormone is administered for five days to an adult rabbit which has been mated and immediately afterwards castrated. On account of the removal of the ovaries, the corpus luteum hormone, which is necessary for the maintenance of pregnancy, is lacking. Without treatment no pregnancy can be maintained. One American rabbit unit is the minimum quantity of hormone which will maintain a normal state of pregnancy in the rabbit under standardized experimental conditions.

As it was outlined, the function of the ovary and the production of its two hormones are stimulated and controlled by the anterior lobe of the pituitary gland. On the other hand, the development and functions of the so-called accessory sex organs such as uterus and vagina are dependent on the hormones of the ovaries. Also the development of the so-called female secondary sex characteristics, such as mammary glands, pubic hair and many others are dependent on the hormones of the ovary, especially the follicular hormone.

There are many indications for the therapeutic usage of the two female sex hormones. Estrogenic hormones have been employed successfully to give relief during the period of menopause and in cases of castration, amenorrhea, dysmenorrhea and migraine. They were also successfully used in cases of gonorrheal vaginitis in children. A promiscuous usage of estrogens must be emphatically discouraged. Any treatment of the before mentioned indications ought

to be carried out under the strict supervision of an experienced physician. The administration of the corpus luteum hormone is indicated especially in the case of habitual abortion. Miscarriage can now be avoided in many cases by systematic treatment with corpus luteum hormone during pregnancy.

The male sex glands, the development and functions of which depend also on the anterior pituitary, are the testes. The so-called interstitial cells of the testes are probably analogous to the Graaffian follicles of the ovaries. Thus they contain the male sex hormone which stimulates growth and functioning of the accessory male sex organs, such as for instance the seminal vesicles, prostate gland and penis. Also the development of the male secondary sex characteristics depends on the male sex hormones. Whereas two physiological types of female sex hormones are known, namely estrogenic hormones and corpus luteum hormone, there exists only one physiological type of male sex hormones.

Two methods for assaying male sex hormones are widely used. The one measures male secondary sex characteristics. It is the well-known comb-growth test which was put on a firm quantitative basis by Gallagher and Koch in Chicago. In capons, in other words, castrated cocks, degeneration of the comb is uniformly observed. Administration of a certain amount of male sex hormone brings about a restoration of growth to normal. The second test method for male hormones measures the growth of accessory male sex organs, for instance the seminal vesicles. Their purpose is the temporary storage of spermatozoa. They are undeveloped in infantile animals. The administration of male sex hormone preparations to infantile male rats will bring about a quick maturation of the seminal vesicles and, of course, also the other accessory sex organs. As will be seen later, there exist several naturally occurring male sex hormones. It should be stated that some of them exert a relatively greater effect on the secondary sex characteristics, such as comb growth, whereas others act preferably on the accessory sex organs, such as seminal vesicles. Therefore the ratio $\frac{\text{seminal vesicle units}}{\text{comb growth units}}$ per weight unit of male hormone preparation differs with each different chemical substance. The clinical application of male sex hormones appears to be restricted. I do not feel authorized to make any definite statements in that line. The Council of Pharmacy and Chemistry of the American Medical Association is of the opinion that the present

clinical data do not yet offer a clear picture concerning the usefulness of male sex hormone preparations.

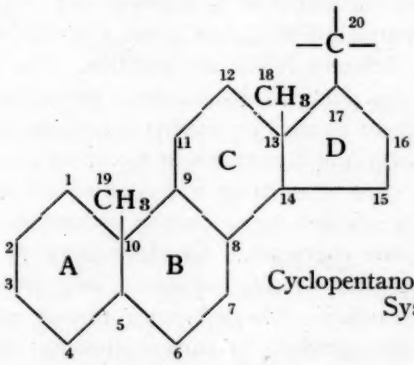
Before entering into a discussion of the chemical aspects of the sex hormones, a few words may be said concerning the adrenal cortex. Sex hormones and cortico-adrenal hormones are chemically closely related. This fact is not so astonishing if one considers the common embryonic origin of sex glands and adrenal cortex. Certain clinical observations which cannot be discussed here show very clearly the interrelationship of these two types of endocrine glands. It must be stated that the adrenal cortex is essential for the maintenance of life. Whereas animals can live without adrenal medulla, the extirpation of the adrenal cortex will always result in death. The administration of appropriate amounts of the hormones of the adrenal cortex will keep adrenalectomized animals alive.

The best test animal for this life maintenance test appears to be the adrenalectomized dog, which requires comparatively little hormone. The dog unit, introduced by Swingle and Pfiffner, is defined as the minimum daily amount of cortico-adrenal hormone per kilo of dog which is able to keep an adrenalectomized dog in an apparently normal condition.

A complicated disease in which the adrenal cortex is involved is Addison's disease. It represents a mainly clinical problem, and can be favorably influenced by treatment with adrenal cortex hormones. The cortico-adrenal hormones are antagonists of insulin insofar as they tend to raise the blood sugar (Diabetogenic action). Furthermore they seem to be connected with the normal salt and water metabolism.

After this rather extensive physiological introduction we turn to the chemistry of the sex hormones and of the cortico-adrenal hormones. There is a large number of estrogenic hormones and also of male sex hormones. Moreover, six cortico-adrenal hormones have been isolated and it can be considered certain that more will be found. It should be stated from the beginning that only one naturally occurring representative of the corpus luteum hormone is known; the chemical structure of this latter hormone appears to be very specific. The chemical specificity of estrogenic hormones, male sex hormones and adrenal cortical hormones, however, is not so great. I shall discuss only the important representatives of each group.

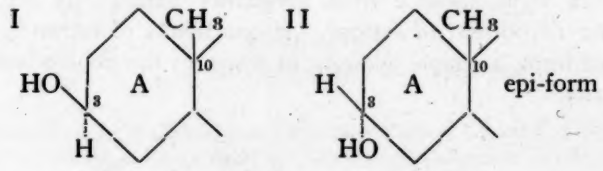
All sex hormones and adrenal cortex hormones are derivatives of the cyclopentano-phenanthrene system. The numbering of the carbon atoms is indicated in the scheme. The six membered rings are called A, B and C; they form the phenanthrene ring system. The five membered cyclopentane ring is called D. If a side chain is attached to ring D at carbon atom 17, the carbon atom of the side chain nearest to carbon atom 17 is called 20, and so on.



Cyclopentano-phenanthrene System

In certain hormones of this group the rings are saturated, in other words, there is no double bond present. Really, I should mention in this connection certain questions of stereochemistry. I realize, however, that a detailed discussion is not of outstanding importance for this lecture. Besides, it would complicate the picture. Therefore this obvious difficulty will be avoided as much as possible.

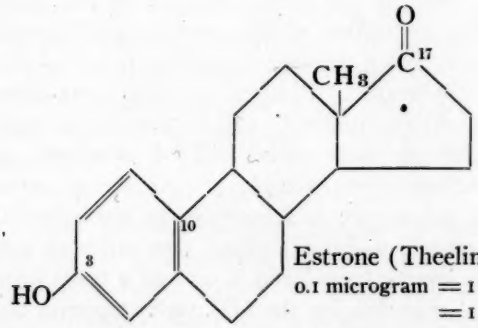
Substituents in these sterol related hormones are preferably attached to carbon atoms 3 and 17. As far as carbon atom 3 is concerned the substituent is frequently an alcoholic OH group. If we consider ring A to form a plane, two different arrangements of the OH group can be considered, a cis and a trans form. That is to say, in the one modification the OH group appears above the plane (i. e. on the same side with the methyl group attached to carbon atom 10), in the other below.



cis/trans isomerism at carbon atom 3

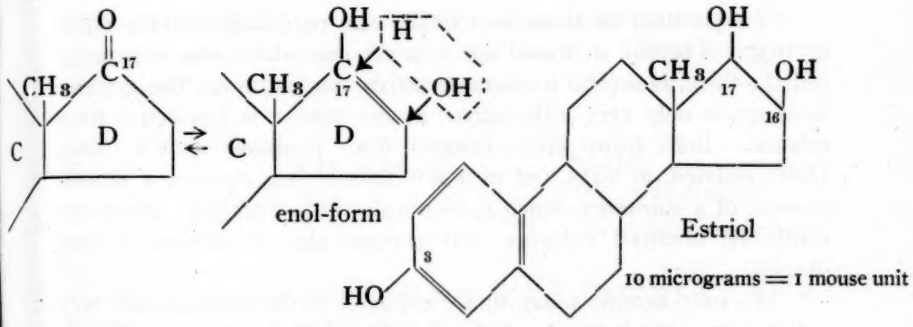
The one of these forms, namely that indicated by formula I, is precipitated by digitonin. The other form gives no precipitate. Naturally this important fact can be utilized for the separation of cis and trans forms in these series. If one wants to designate that isomer which is not precipitated by digitonin, one frequently puts before the chemical name the prefix "epi."

Such stereo-isomerism at carbon atom 3 is impossible, of course, if ring A has the structure of a benzene ring. In this case no hydrogen atom is attached to carbon atom 3 besides the OH group; therefore no two different forms are possible. The estrogenic hormones which we are going to discuss first, belong to this type. In these hormones there is also no methyl group at carbon atom 10. Doisy in this country and Butenandt in Germany succeeded at about the same time in 1929 in isolating a crystalline hormone from pregnancy urine which is called today estrone because it produces estrus and possesses ketone character. An older name is theelin. Fractions of one microgram of this substance were able to produce a positive estrous reaction. The substance turned out to possess a phenolic OH group attached to carbon atom 3; carbon atom 17 forms a keto group.



Estrone (Theelin)
0.1 microgram = 1 mouse unit
= 1 Internat. unit

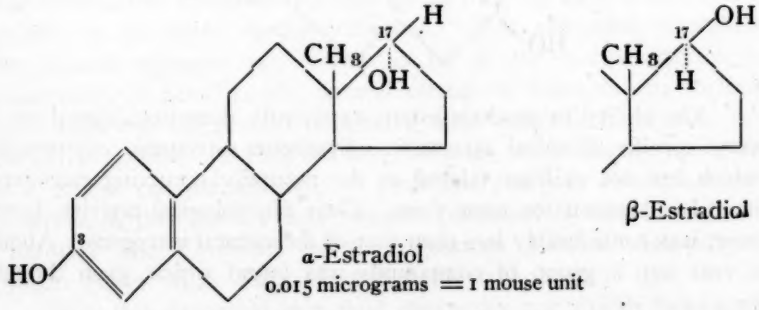
A hydrate of estrone, the so-called estriol, was isolated by Marrian in 1930 likewise from pregnancy urine. Its activity is only about 1/100 that of estrone. If one thinks of estrone existing as an enol-form, a simple addition of water to the double bond may yield estriol.



It is possible to dehydrate estriol in the laboratory to estrone by means of potassium bisulfate. The reverse reaction has not been achieved in the test tubes; but it is certainly a common biological process.

Estriol occurs in human pregnancy urine in the form of the glucuronidate, as was established by Marrian in 1936. This compound, however, has only about one-seventeenth the potency of the same amount of uncombined estriol.

As is known, the hydrogenation of a ketone leads to a secondary alcohol. The hydrogenation of the keto group of estrone was first carried out in 1933 by Schwenk and Hildebrandt. The reduction product is called dihydro-estrone or estradiol; it represents a mixture which is easily explainable on the basis of what I have mentioned before. The hydroxyl group at carbon atom 17* can be attached either in cis or in trans configuration. The reduction product is a mixture of both forms.

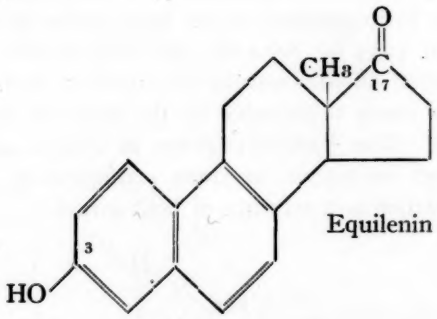


* Other cases of stereoisomerism besides those at C_3 and C_{17} have been observed for instance at C_5, C_9 and C_{20}. They are not discussed in this lecture.

A separation of these two forms was published by Butenandt in 1937. Thereby it turned out that the one which was arbitrarily called α-form, is several times more active than estrone. The β-form, however, is only very little active; at any rate, it is less active than estrone. Both forms were isolated from pregnant mare's urine. Doisy isolated, in 1935, out of a few tons of hog ovaries, a certain amount of a substance which is identical with α-estradiol. More recently he obtained evidence that estrone also is present in hog ovaries.

We may assume today that α-estradiol is the original and very potent estrogenic hormone of the Graaffian follicles, whereas estrone is formed by dehydrogenation of the former.

There occur several other estrogenic hormones in Nature. They differ from those which I have discussed insofar as not only ring A, but rings A and B are unsaturated and consequently form a naphthalin structure. Their physiological activity is not very great and therefore they will not be discussed. The best known representative is equilenin which was isolated from pregnant mare's urine by Girard in 1932.*

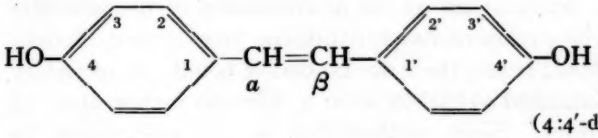


Equilenin

The ability to produce estrus apparently does not depend on a very specific chemical structure. Synthetic estrogenic compounds which are not at least related to the naturally occurring estrogens have been known for some time. Their physiological activity, however, was considerably less than that of the natural estrogens. About a year ago a group of compounds was found which, even though

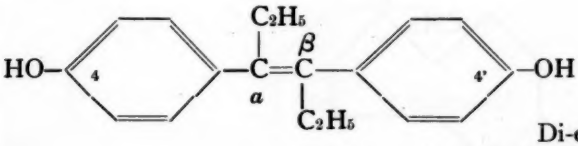
* An interrelationship exists between the chemical structures of certain sex hormones, especially estrogens, and those of carcinogenic agents. A discussion of this aspect cannot be included in this lecture.

being chemically completely different from natural estrogens, compares favorably with their physiological activity. These compounds are derivatives of 4:4′-dihydroxy-stilbene.



Stilbestrol
(4:4′-dihydroxy-stilbene)

By far the most potent substance is 4:4′-dihydroxy-α, β-diethyl-stilbene.



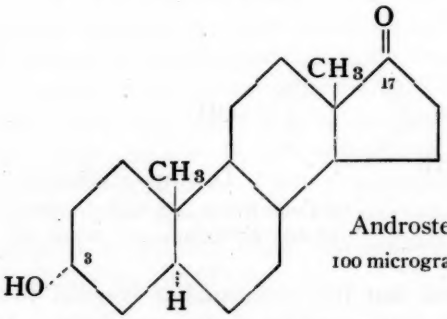
Di-ethyl-Stilbestrol
(4:4′-dihydroxy-α, β-diethyl-stilbene)
0.03-0.05 micrograms = 1 mouse unit

Comparative tests showed that this compound is between two and three times as potent as estrone under similar conditions. It might be mentioned in this connection that the most powerful natural estrogenic hormone, the α-estradiol, is about six times as effective as estrone.

In view of the fact that 4:4′-dihydroxy-stilbene is the mother substance of a series of estrogenic agents, the discoverers of this group, Dodds and Robinson, suggest that it may be termed stilbestrol. The most active compound of this group thus far known has consequently to be called diethyl-stilbestrol. This substance resembles the natural estrogens not merely as far as the estrus reaction is concerned. It acts like the natural estrogenic hormones in various other respects. At present it is being tried out on a large scale for clinical purposes. In England and Germany it is already available as a commercial preparation. A preliminary report on clinical experiences in this country was recently published by the Council on Pharmacy and Chemistry of the American Medical Association. (Journ. Amer. Med. Assoc., 113, No. 26, 2312, 1939.)

After this excursion in a field chemically not strictly belonging to our topic, we shall proceed to the male sex hormones. The first crystalline preparation of this kind was isolated by Butenandt from

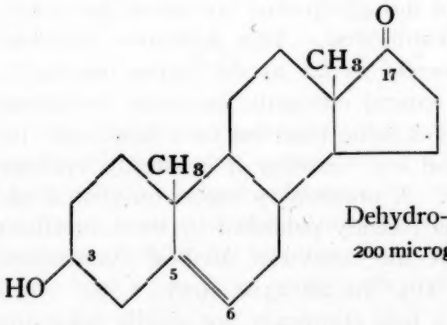
the urine of males in 1931. He isolated fifteen milligrams of androsterone from 15,000 liters of men's urine. Today we know that the urine of stallions is a much better source for androsterone. I cannot go into details as far as the determination of the structure is concerned. The cyclopentano-phenanthrene ring system is completely hydrogenated; hence, there are no double bonds. A secondary alcohol group is attached to carbon atom 3, whereas carbon atom 17 forms a keto group. Since androsterone is not precipitated by digitonin, the OH group at carbon atom 3 must be in epi-position.



Androsterone

100 micrograms = 1 comb growth unit
= 1 Internat. unit

Butenandt isolated a second, but less active male sex hormone from male urine in 1934. The substance proved to contain a secondary alcohol group and a keto group at exactly the same places as androsterone; but there were two hydrogen atoms less and consequently the molecule contains one double bond. The chemical structure turned out to be the following:

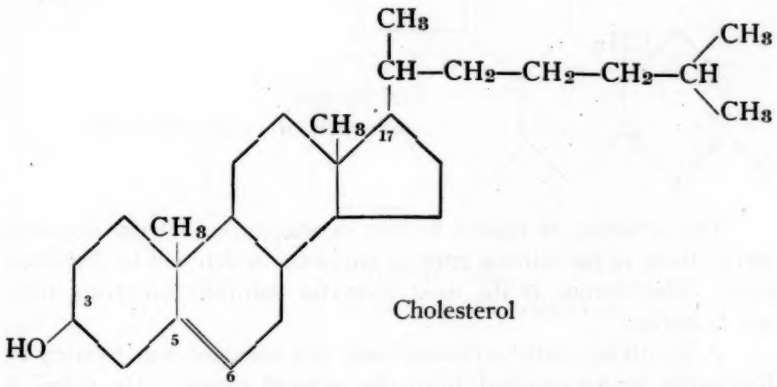


Dehydro-iso-Androsterone

200 micrograms = 1 comb growth unit

It is called dehydro-iso-androsterone. The prefix "iso" is given because the configuration of the OH group at carbon atom 3 is

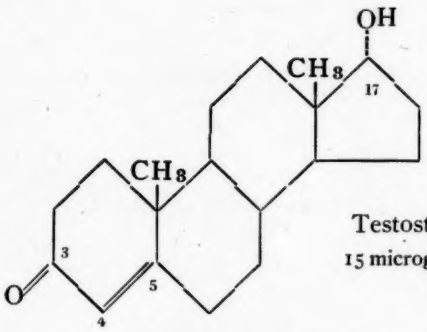
different from that in androsterone. Consequently dehydro-iso-androsterone gives a precipitate with digitonin. The structure and configuration of this compound is completely analogous to that of cholesterol.



Cholesterol

It is very probable that cholesterol is the mother substance of dehydro-iso-androsterone and that the latter is formed by a biological oxidation of cholesterol whereby the whole side chain is eliminated. Under certain precautions the oxidation of cholesterol to dehydro-iso-androsterone can also be performed in the chemical laboratory. This fact is today the basis for the artificial preparation of several sex hormones.

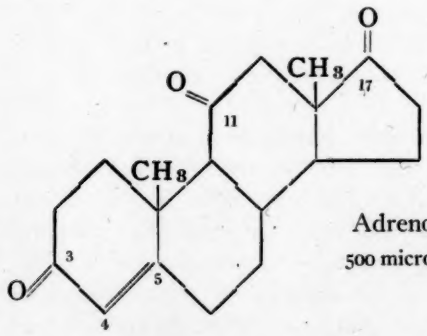
It has been known for a rather long time that extracts obtained from testes exert a rather great effect on the seminal vesicles, if one compares it with that exerted on the comb growth. In this respect testes extracts differed distinctly from urine extracts. Furthermore, Gallagher and Koch found as early as 1934 that the activity of testes extract is destroyed by treating it with alkali; under equal conditions the activity of urine extract is not changed. All this indicated that the testis hormone is different from the male hormones of urine. Laqueur and collaborators isolated in 1935 from testes extract traces of a crystalline substance which matched the before mentioned observations. It was called testosterone and turned out to be an α, β-unsaturated ketone. The formula is the following:



Testosterone
15 micrograms = 1 comb growth unit

The structure is related to that of the corpus luteum hormone and to those of the adrenal cortical hormones which will be discussed later. Testosterone is the most powerful naturally occurring male sex hormone.

A fourth naturally occurring male sex hormone was isolated by Reichstein in Switzerland from the adrenal cortex. He called it adrenosterone. The comb growth activity is only about one-fifth that of androsterone. The chemical structure is very likely the following:

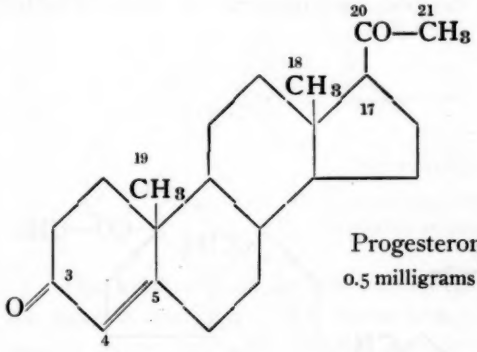


Adrenosterone
500 micrograms = 1 comb growth unit

It is the only compound with three oxygen atoms in the series of naturally occurring male sex hormones.

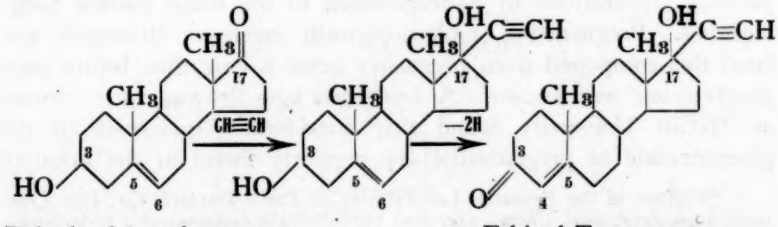
Three laboratories were successfully engaged in isolating the corpus luteum hormone, namely those of Butenandt and of Slotta in Germany and that of Wintersteiner and W. Allen in this country. Only one chemical individual of this hormone was isolated; its chemical name is progesterone. The chemical structure is closely related to that of testosterone. Therefore it is understandable that big doses

of testosterone or chemically related compounds can bring about a certain corpus luteum hormone effect. This effect is very slight, however, in comparison with that of progesterone. The structure of progesterone is the following. The resemblance to that of testosterone is obvious.



Progesterone
0.5 milligrams = 1 rabbit unit

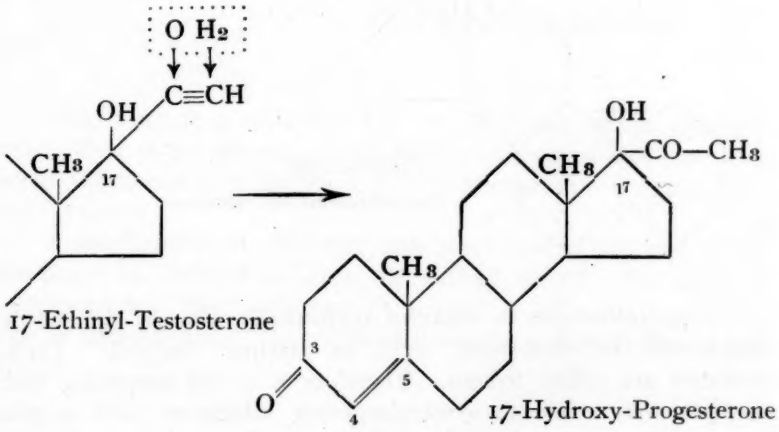
Progesterone can be obtained synthetically whereby the sterols stigmasterol or cholesterol serve as starting material. These syntheses are rather tedious. Therefore it is not surprising that attempts were made to synthesize other substances with corpus luteum hormone activity. But all these attempts have met with failure until rather recently when a synthetical substance was described which is astoundingly active. Starting material for this synthesis is dehydro-iso-androsterone which, as I mentioned, can comparatively easily be obtained by oxidizing cholesterol. Dehydro-iso-androsterone is treated with acetylene whereby a side chain with a triple bond is introduced. Dehydrogenation at carbon atom 3 yields a remarkably effective substance:



Dehydro-iso-androsterone

17-Ethinyl-Testosterone
(Anhydro-Hydroxy-Progesterone, Pregneninonol)
1.5 milligrams = 1 rabbit unit

Injected subcutaneously this substance possesses one-third of the activity of progesterone. The outstanding property of this compound is its activity when given orally. Whereas sixty milligrams of progesterone are completely ineffective when given by mouth, four milligrams of this synthetic substance yield an outspoken positive result. It may be that in the body one molecule of water is added to the triple bond.

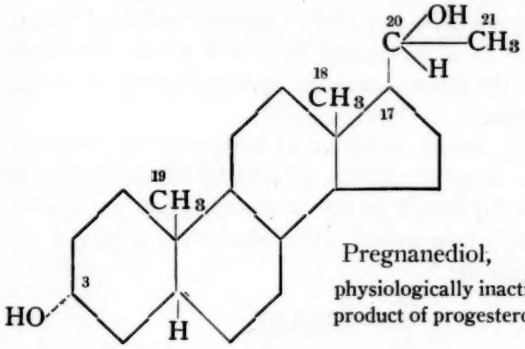


Thus a 17-hydroxy-progesterone would be formed which might represent the real effective substance. It would not be surprising if 17-hydroxy-progesterone were isolated some day from corpora lutea or the adrenal glands.* It ought to be mentioned that the orally effective progestational compound (17-ethinyl-testosterone) is now on sale in this country.

I should mention one product into which progesterone is apparently transformed by hydrogenation in the body, namely pregnanediol. Pregnanediol is physiologically inactive. Butenandt isolated this compound from pregnancy urine a long time before pure progesterone was known. A few years ago Browne and Venning at McGill University found that considerable quantities of the glucuronidate of pregnanediol are regularly found in the urine of

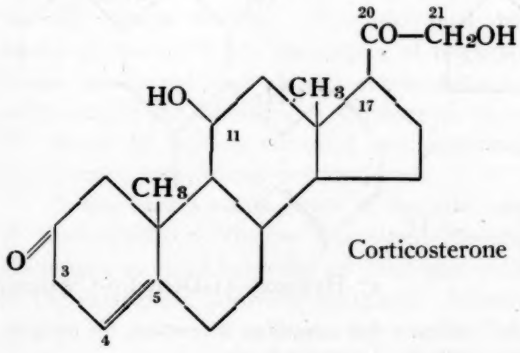
*Pfiffner in the Research Laboratories of Parke-Davis & Co., just (January, 1940, *Jour. Biol. Chem., 132,* 461) published the isolation of a 17-hydroxy-progesterone from the adrenal glands. It is apparently physiologically inactive. This finding must not necessarily be inconsistent with the theory discussed above. The possibility remains that Pfiffner's 17-hydroxy-progesterone and that formed from 17-ethinyl-testosterone in the body differ regarding the configuration at carbon atom 17.

women during the second half of the menstrual cycle, which is, as was mentioned, under the influence of the corpus luteum.



Pregnanediol,
physiologically inactive excretion product of progesterone

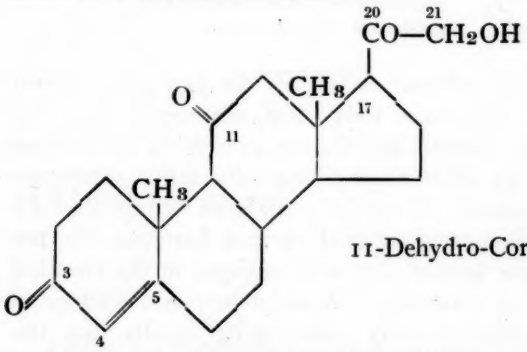
The hormones of the adrenal cortex are the last group which we have to consider. We know today that not merely one, but several compounds with "cortin" activity are present in the adrenal glands. No less than six different physiologically active substances have thus far been obtained. It can be considered certain that the most active naturally occurring adrenal cortical hormone has not yet been isolated. Three laboratories were engaged in the chemical study of adrenal cortical hormones. Wintersteiner and Pfiffner at Columbia University obtained very encouraging results, but unfortunately they were hampered by a lack of sufficient quantities of adrenal glands. Kendall and Mason at the Mayo Clinic carried the work somewhat further; they have used until now more than 100 tons of adrenal glands. Reichstein in Switzerland outdistanced both groups of workers. He isolated the first crystalline compound with definite cortin activity and called it corticosterone. Its chemical constitution is very likely the following:



Corticosterone

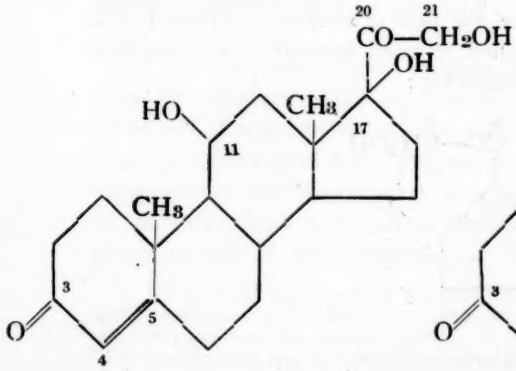
It is evident that this structure is closely related to that of progesterone, the corpus luteum hormone. Therefore it is not very surprising that recently progesterone which was originally isolated from corpora lutea was found also to be a constituent of the adrenal glands. Corticosterone contains two more alcoholic hydroxyl groups than progesterone; one is a secondary hydroxyl group at carbon atom 11 of the nucleus, the other a primary hydroxyl group at carbon atom 21 of the side chain.

Another compound, almost as active as corticosterone, was isolated by Kendall. Its structure differs from that of corticosterone insofar as the alcoholic hydroxyl group at carbon atom 11 appears to be dehydrogenated to a keto group. Therefore the compound was called dehydro-corticosterone.*

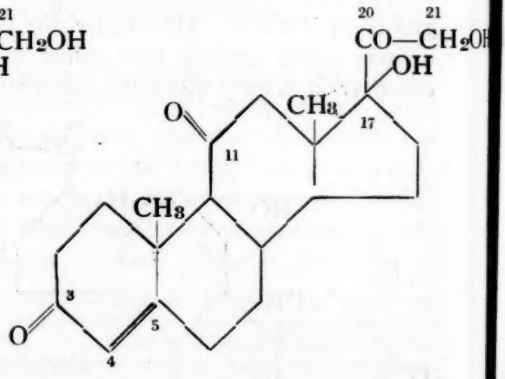


11-Dehydro-Corticosterone

Two other adrenal-cortex hormones are derived from corticosterone and dehydro-corticosterone respectively, insofar as a hydroxyl group is present at carbon atom 17.



17-Hydroxy-Corticosterone

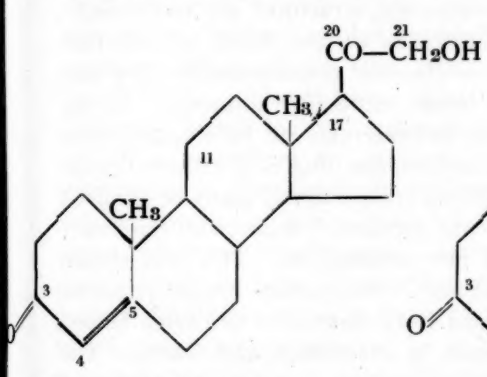


17-Hydroxy-11-Dehydro-Corticosterone

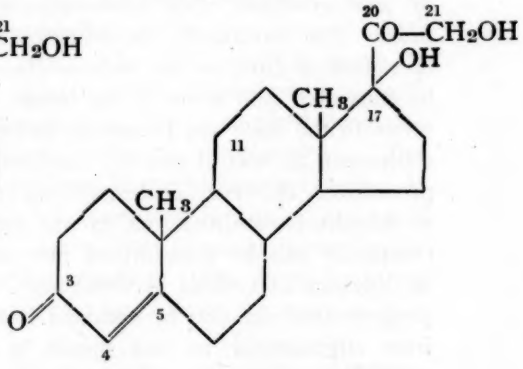
* The prefix "de" or "des" indicates that something is removed, for instance hydrogen or oxygen; therefore "dehydro-", "desoxy-", etc.

It is not yet exactly known how far the physiological activities of these four compounds differ.

Two other substances obtained from the adrenal cortex contain no oxygen at carbon atom 11. Their structures are as follows:



11-Desoxy-Corticosterone
(21-Hydroxy-Progesterone)
synthetically obtainable



17-Hydroxy-11-Desoxy-Corticosterone

The one is called desoxy-corticosterone because it differs from corticosterone insofar as there is no hydroxyl group at carbon atom 11. It is in the life maintenance test the most active adrenal cortical hormone. The other compound differs from desoxy-corticosterone insofar as there is an additional hydroxyl group at carbon atom 17.

If one looks at the chemical structures of all six adrenal cortical hormones one realizes that they have two features in common: first, the keto group and the double bond in ring A; second, the keto group and the primary alcohol group, in other words the ketol group, in the side chain. These features of the molecule are essential for adrenal cortical activity. The additional oxygen atoms at carbon atoms 11 or 17 modify the degree of physiological action. It ought to be mentioned that desoxy-corticosterone can also be obtained artificially in the laboratory. Cholesterol serves as starting material. By means of various chemical manipulations it can eventually be transformed into desoxy-corticosterone.

A few more words ought to be said concerning the possibility of synthesizing the before mentioned hormones. Recently W. E. Bachmann at the University of Michigan published a total synthesis of the estrogenic hormone equilenin. Since equilenin contains the

naphthaline ring structure, it is not surprising that a naphthalin derivative served as starting material for this synthetic work. Equilenin in turn can be transformed into the other estrogenic hormones. The remaining steroid hormones will hardly be accessible by total synthesis; their stereo-chemical structures are too complicated. But fortunately the structure of certain sterols is such that by means of more or less tedious chemical transformations they can be converted into some of the before mentioned hormones. In the series of the male sex hormones androsterone can be obtained from cholesterol as was shown by Ruzicka, but this is a rather difficult procedure. However, cholesterol can comparatively easily be oxidized to dehydro-iso-androsterone as was mentioned before, and this latter compound can be transformed into testosterone. This was shown by Ruzicka as well as by Butenandt. The corpus luteum hormone progesterone can also be obtained from cholesterol or, much better, from stigmasterol, as was shown by Butenandt and others. The possibility of obtaining testosterone and progesterone by means of this kind of synthesis is extremely important, because these hormones can be obtained from the respective glands only in very poor yields. The same holds for the transformation of either cholesterol or stigmasterol into desoxy-corticosterone.

Another interesting chapter is the activation of sex hormones and cortico-adrenal hormones. I can only give a very brief idea. A normal endocrine gland must be supposed to keep up a slow, steady secretion which maintains a threshold concentration in the circulation but avoids wasteful or harmful excess. The organism is able to utilize only a limited amount of hormone at a time. If hormone is injected, it is usually absorbed rapidly and thereafter utilized, destroyed or excreted. In these circumstances the concentration in the blood will be highest soon after injection, and will then fall away until a sub-effective concentration is reached. If an overdose of hormone is injected the organism will eliminate the excess by destruction or excretion. The general aim should be to ensure the continuous availability of the optimal concentration in the blood stream. Consequently a certain excessive amount of hormone will usually prove more effective when spread over frequent injections rather than when given in one single injection. It is obvious that very frequent injections are troublesome and sometimes detrimental in animal experiments as well as in human therapy. Parkes of the National Institute of Medical Research in London created a depot

of hormone in the body by implanting tablets under the skin. This ensures a slow and economic absorption over a rather long time. It could be shown that the size of tablet decreases very gradually and that the effect is maintained over weeks and months. Estrogenic hormones, such as estrone, as well as male hormones, such as testosterone, respond to this application. Also the cortico-adrenal hormones behave in the same way. This was recently shown by Thorn in the Johns Hopkins Hospital, who treated patients with Addison's disease by the implantation of desoxy-corticosterone tablets. Parkes believes that the same holds for progesterone. This latter belief is very important because of the following reason: As will be seen later, esterification of hormones is also a means of increasing their effectiveness. Since the chemical structure of progesterone precludes an easy esterification (there is no hydroxyl group) the tablet technique appears to be of value for cases of prolonged progesterone treatment.

An esterification of sex hormones, such as estrogens, androgens and cortico-adrenal hormones can under certain conditions enhance the effect of the non-esterified hormones. As I see it, the effect may depend largely on the rate of hydrolysis of the ester in the body. If the rate of hydrolysis concurs with the rate of utilization of the liberated hormone by the organism, we may obtain an optimal effect. As far as testosterone is concerned it can be said that especially the lower fatty acid esters, for instance the propionate, are highly effective. It is not opportune to discuss the change of activity brought about by the esterification of estrogens. There certainly are outspoken effects, especially on the length of the estrus reaction and on the growth of the uteri. It is difficult, however, to review the available data in an easily understandable manner. Last, but not least, the effect of the adrenal-cortex hormones can also be increased by esterification.

You will have concluded from my report that sterols, such as for instance cholesterol, sex hormones and adrenal cortical hormones are closely interrelated, at least from a purely chemical point of view. It is very likely that these substances also form a biochemical system, that is to say, one substance can be transformed into the other in the body. We do not know as yet whether the sex hormones are intermediates in the formation of the sterols which contain a rather long side-chain. It may also be the other way around, namely

that the sterols are the primary substances, whereas by oxidation the side chain can be shortened to the progesterone or adrenal cortex hormone type, and last but not least, to the type of male hormones and estrogenic hormones. Painstaking biological experiments will have to be carried out before an accurate scheme of the biochemical interrelationship of these compounds can be set up.

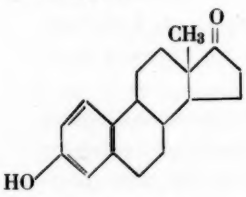
List of Commercial Preparations Available in the United States

(This list is not claimed to be complete; only chemically defined substances are included)

Female Sex Hormones

A. Estrogenic

1. Estrone



Amniotin — E. R. Squibb & Sons (Ampules; Pessaries; Capsules)

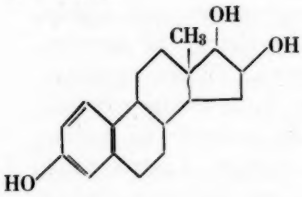
Menformon — Roche-Organon, Inc. (In Oil; Tablets)

Theelin — Parke-Davis & Company (In Oil; Aqueous)

Estrone — Abbott Laboratories (In Oil; Vaginal Suppositories)

Estrone — Eli Lilly & Co. (Ampules; Suppositories)

2. Estriol



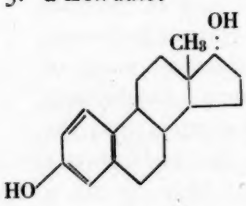
Theelol — Parke-Davis & Company (Kapseals)

Emmenin — Ayerst, McKenna & Harrison (=Estriol Glucuronidate)

Estriol — Abbott Laboratories (Capsules)

Estriol — Eli Lilly & Co. (Pulvules)

3. α-Estradiol

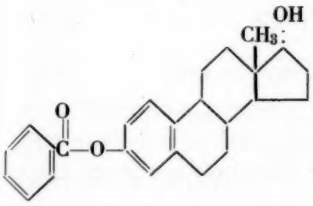


Dimenformon — Roche-Organon, Inc. (Tablets)

Progynon-DH — Schering-Corporation (Tablets; Solution; Suppositories; Ointment)

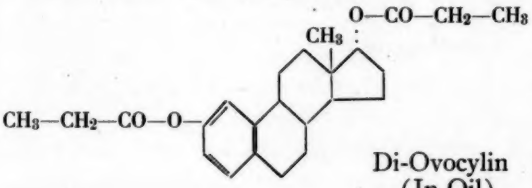
Ovocylin — Ciba Pharm. Products, Inc. (Tablets; Suppositories; Ointment)

4. α-Estradiol Benzoate



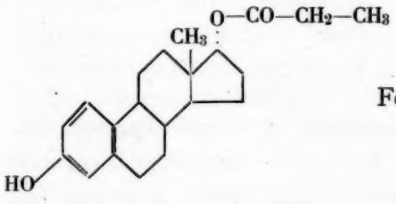
Dimenformon Benzoate — Roche-Organon, Inc.
Progynon-B — Schering-Corporation
Ben-Ovocylin (In Oil) — Ciba Pharm. Products, Inc.

5. α-Estradiol Dipropionate



Di-Ovocylin (In Oil) — Ciba Pharm. Products, Inc.

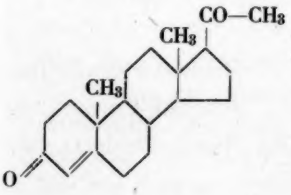
6. α-Estradiol-17-Propionate



Follacro — Schieffelin & Co.

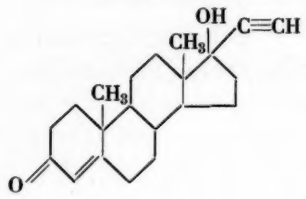
B. Corpus Luteum Hormone

1. Progesterone



Proluton — Schering-Corporation
Progestin — Roche-Organon, Inc.
Lutocylin — Ciba Pharm. Products, Inc.

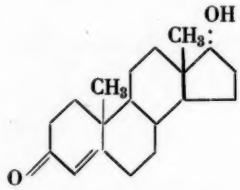
2. 17-Ethinyl-Testosterone
(Anhydro-hydroxy-progesterone; Pregneninonol)



Pranone — Schering-Corporation

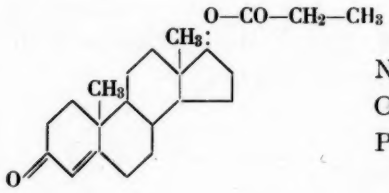
Male Sex Hormones
(Androgenic)

1. Testosterone



Oreton-F (Ointment) — Schering-Corporation

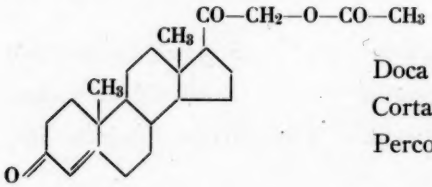
2. Testosterone Propionate



Neo-Hombreol — Roche-Organon, Inc.
Oreton — Schering-Corporation
Perandren — Ciba Pharm. Products, Inc.

Adrenal Cortex Hormones

Desoxycorticosterone Acetate



Doca — Roche-Organon, Inc.
Cortate — Schering-Corporation
Percorten — Ciba Pharm. Products, Inc.

SOLID EXTRACTS

By Ivor Griffith, Ph. M., Sc. D., F. R. S. A.

Despite the form in which this information is presented it may be accepted as trustworthy and up-to-date. Original sources are not listed but they may be obtained upon request.

A Challenge to the Imagination: Iodine and Anthropology. If the Garden of Eden was somewhere in the region of the Gobi Desert, as is alleged by some, Adam and Eve, even after the primal sin had sent them commuting, lived on an iodine-low diet. No more inland spot could have been chosen for man's beginnings, and such of his children as remained long (several myrennia) in that vicinity have held on to their slit-eyed Mongol features. The Mongolian face may or may not have been man's original appearance. If it was, then all artists to date have neither depicted nor oriented Adam and Eve in conformity with physiologic *conjecture!*

Uneasy men, with strangely active and perhaps pathologic thyroid, who migrated shoreward and westward ultimately lost their Mongolian appearance, lost it permanently, except where today through some freak of physiology a thyroid gland underfunctions, and lacking iodine's influence, there is a reversion to Mongoloid features and often Mongoloid characteristics. Consider the cretin, *one of us,* and on the other hand consider the composed sinesque hypothyroid.

Continuing our iodine wondering and wandering, is it possible that the attenuation of Mongolian features and attributes has been a function of time and migration as well as of water and soil and food. For instance consider the color and feature attenuation beginning with the Chinese, thence southwestward to the Thibetan, the Thai, the Indian, the Arab, etc., northwestward to the Lapp, the Finn, the Siberian, the Eskimo, etc., then east to the Inca, the American Indian, etc. One could almost graph the eye slant variation and so trace and track the time and place factors. Eyes have always been the thyroid signals. The pop-eyed are thyroid overdone, the slit-eyed, the slant-eyed, and the sunk-eyed may be under-iodated. Someone argues that the

Eskimo has ample iodine in the sea food he eats, but we suggest, in rebuttal, that his fathers had remained so long inland that the complete wiping out of Mongoloid features will be a matter of more millenia. To get the thyroid operating on the same cycle in the Eskimo as it does in the Caucasian is a province of time and location, for more than likely the Caucasians (especially the Aryans!!) have been close to iodine supplies much longer than have God's frozen children!

To the laboratorian B. M. R. means *basal metabolic rate,* and in the indirect estimate of the functioning of that little iodine factory with big responsibilities, called the thyroid gland, a determination of the B. M. R. affords something of a diagnostic picture. Thus the normal hits the 100 mark, the over active thyroid runs up beyond the hundred, and the under active below, sometimes way below. Anthropologically there might be some value in determining the B. M. R. of a typical on-location Mongolian (not a Mongoloid), of a Lapp, an Eskimo, a Finn, although, to the latter, B. M. R. might only mean *Bring More Russians!!!*

And since this day's ink seems to be iodine, it is interesting to recall that the chemist's crucible is now turning out at will, a clinically proven synthetic equivalent to the four iodine cornered complex delivered by that ounce of neck-located thyroid gland. Synthetic thyroxine, as first prepared by Harington and Barger, despite its cumbersome two-ringed formula is nearly seventy per cent. rich in iodine. To prove its equality to the natural product the investigators pushed a weak solution of it into the circulation of a few patients with low metabolic rates (54 to 60) and the body promptly answered by smacking the bell at the hundred mark.

And mind you, of actual iodine, in active body use, only a trace is needed, a mere widow's mite;—but what a mighty mite!!

Listen! The high tide of iodine in the blood is about 1 grain of iodine to 10 million grains of blood or less than a hundredth (1/100) of a grain in the entire circulation. The iodine reservoir in the body, namely, the store room of the thyroid factory, only holds one-third of

a grain (about 25 milligrams), and in order to keep this reservoir full the normal human being has only to consume per day, in his *air,* or food or drink, less than a thousandth of a grain of iodine. No wonder some people believe in Homeopathy. It seems that the Great Spirit did!!

Moral: Irrespective of religion make Friday a fry-day—of salt water crustaceans or fish!

This terrestrial sphere is rich in iodine! Most all sea organisms, plant and animals are heavy with it. Consider the sponge. In some tropical species the ash will contain from 8 to 14 per cent. of the element. This ash was given as a medicine, an *official* medicine, in the early part of the nineteenth century when the best "study of mankind was man," not the guinea pig! Even the humble oyster, whether brought up in beds, well-aired or not, harbors his share of iodine. Sea water itself contains about 1/300th of a grain of iodine to the gallon, yet oddly the great Salt Lake of Utah while containing five times as much salt as ordinary sea water shows only about 1/200th grain of iodine to the gallon. Which proves after all that iodine is a sea-going simple, and at its best only an excursioning land-lubber.

Certain imaginations have conjured the claim that all life was once marine or submarine—that the antecedents of every creature now living, like Venus of old, once lolled in a luke-warm sea. One of the ariadnic threads wherewith they bind their arguments is in the remarkable comparison which they make between animal blood and sea water. Blood plasma indeed is in salt content, chloride, phosphate, iodine and other substances, very like sea water, and the ratios are remarkably alike. The contention of such conjecturers is that whereas we were once limpid jelly fish floating lazily on the dank primeval ocean, we are now so evolved and involved that a share of the sea floats diligently within us, its ebb and flow in every heartbeat.

But so it is, with the mouse and the louse!! So what??

And is the matter of lassitude, of the complacent attitude of the typical Oriental of long inheritance, another of iodine's errors of omis-

sion? Listen again! The purpose of the body's iodine factory, the thyroid gland seems to be to control the dynamy of living, in the physico-chemical sense. A thyroid gland which is over producing accelerates every body function—opens wide the drafts of the fiery furnaces wherein our food and flesh are burnt away to ashes and to energy, over-sensitizes our nervous structures and over-speeds our blood stream. Everything done is over done and death comes that much sooner!

But the gland that is under-producing slows up the system, underfires the powerhouse and soots and shuts the chimneys, it underworks the brain and makes it dull and drowsy. Lack of its normal secretions undermines the nerve and muscle, the victim is awkward and clumsy, the blood is underfed and so invites infection. Everything done is underdone and even death comes lazily.

Thus are fifty years of Europe like a cycle in Cathay!!!

And thus too are we the trivial toys of a mite of iodine. No wonder the chemists have given this element the symbol I. It can well afford its egotistic elemence.

A Variety of Useful Inks

As a standard ingredient of many types of inks the value of glycerin has long been recognized because of its exceptional solvent powers, hygroscopicity, low freezing point and other important physical properties. Writing, copying, hectograph, stamp-pad, recording, mimeograph, printing, lithographing and a host of other inks are benefited by the inclusion of this unique fluid.

To illustrate the versatility of glycerin in this connection the formulas of a few typical and a few out-of-the-ordinary inks are presented. They are, in general, easy to prepare and used for the purposes indicated.

Finger Print Ink

Glycerin	112 parts
Ferric chloride	10 parts
Carbon black (colloidal)	1 part
Acetone	90 parts

Fabric Marking Ink

Copper sulfate	20 parts
Dextrin	10 parts
Aniline chloride	30 parts
Glycerin	6 parts
Distilled water	100 parts

Mix in order given.

Ink for Printing on Wet Lumber

Starch	90–100 parts
Glycerin	8– 16 parts
Vinegar	60– 70 parts
Coal tar color	sufficient

Water-Soluble Printing Ink

Glycerin	100 parts
Gum arabic	50 parts
Water-soluble dye	10 parts

Invisible Ink

Cobalt chloride	3 parts
Water	64 parts
Glycerin	1 part

Stencil Ink

Prussian blue	2 parts
Lampblack	1 part
Gum arabic	3 parts
Glycerin	sufficient

Mix the powders and make into a suitable paste with glycerin.

Stamp-Pad Ink for Paper

Coal-tar dye	10–20 parts
Glycerin	600 parts
Water	200 parts
Alcohol	200 parts

BOOK REVIEWS

Done by persons, unafraid to upbraid, but perfectly willing to give praise where praise is really due.

Hair Dyes and Hair Dyeing; Chemistry and Technique. The first edition was by H. Stanley Redgrove and Gilbert A. Foan. In this revision the latter, deceased, is replaced by J. Bari-Woollss. 206 pages, 8 plates and numerous illustrations. Price: $5.00. The Chemical Publishing Co., Inc., New York City.

This work is the joint enterprise of the well informed cosmetic scientist, Redgrove, and the practical beautician, Bari-Woollss. From such a combination of the scientist and artist one would naturally expect a serviceable book.

One is not disappointed!

There is really not much that is *new,* brand new about the book, but then there has been very little of strikingly new departures in these phases of cosmetology, particularly trichochromatology.

When someone comes along with a quinonoid organic structure, rich in tricho-tinctorial power, and with no nitrogen to give rise to quinone-di-imine and similar toxic complexes, then we shall hail the event as new.

But so long as those who hair-dye have still to rely on henna, walnut, metallic pigments and toxic coal tar compounds, there is no cause for undue enthusiasm.

Yet there has been progress in the practice. No longer does a peroxide blonde look as if she wore a burlap halo, and no longer does the permanent wave look like an Appian pavement. Indeed the beauty parlor has done a commendable job in the improvement of its technic and performance!

Ovid, somewhere in his metamorphic gossip says:

> "Long since, I warned you not to use that bleaching lye,
> Now there is left no single curl to dye."

The modern beauty-shop does a far better job than Ovid intimates, thanks largely to the work of persons like Foan, Bari-Woollss, Leftwich, Goodman, Nessler, Wall, Poucher, Redgrove, and many others.

The book first treats, in a readable, elementary fashion (very elementary indeed, so far as the protein chemistry of hair is concerned), of the structure and pigments of hair.

Then in part two, it comprehensively and discriminately (pointing out the hazards) surveys the existent dyes, bleaches and decolorants, and in part three, it carefully and thoroughly discusses the *art* of hair dyeing.

A good bibliography is appended. Although formulas are generally in the metric system, Americans should recall that the book is British in origin and that the Imperial system is the metrologic basis of all the recipes.

By whatever name you call it, canitology, polycapilchromy, trichochromatology, or just plain hair dyeing, a sufficient of this cosmetic practice is done candidly as well as clandestinely to warrant the need for authoritative high grade books on the subject.

As before stated, this book is just such a reliable, comprehensive and practical contribution.

IVOR GRIFFITH.

The Merck Index. Fifth Edition. By Joseph Rosin, C. V. Addinall and Alfred I. Cone and others of the Merck staff. 1060 pages. Leatheroid bound. 1940. Merck & Co., Rahway, N. J. Price: $3.00.

One of the best compliments ever paid to this valuable work was in the routine advice of the late Dean Charles H. LaWall. He would always to his inquiring assistants say: "Look it up, first of all, in Merck's Index—if it isn't there, look everywhere else."

And over its several editions The Index has earned the compliment, and particularly so the one now being reviewed.

More comprehensive than ever, its table of contents surveys a discriminate, practical context, sensibly arranged. And Merck's Index is an authoritative compilation! It always has been that, and knowing the character of its mentioned compilers one would scarcely expect the present edition to be else than authoritative.

The alphabetically arranged fore-part is enlarged and brought remarkably up to date (except that it does not include the second U. S. supplement). On the other hand, with supplements coming as frequently as they do, how could one ever expect conclusive inclusion.

The reviewer notes the up to the minute addition of surface tension depressants (gardinol, etc.), the sex hormones and precursors (e. g., *Stilbene,* discovered by Laurent in 1845!!!), the vitamins, the new solvents, etc. Structural formulas are given for important organics. The compilers have seemingly recognized, in more than priority in print, the importance in use of part one of the Index. Up-to-dateness is also evidenced in the survey of certified dyes and in the tables of indicators. The mineralogist and geologist, amateur and professional, will find use for the expansive table of minerals and their properties.

An author's name series (4510 items) of chemical, clinico-chemical reactions, tests and reagents, a compilation largely achieved by joining sections appearing in Merck's Report, after translation from the German, it *without question* the best of its kind available in the language. Even Merck's Index is glorified by it, and the index of this section of the Index is particularly good.

Other sections are devoted to antidotes, formulas for stains and medical equivalents, physical constants in solubilities, density, refractive indices, etc., all useful and all contributing to making this new edition of Merck's Index a real *"vade mecum"* to pharmacist, chemist, nurse and physician, indeed to all persons engaged in the broad services of science. To state that it deserves a place on the library shelf of every such person is an unwitting malapropism. Merck's Index should scarcely ever remain on the shelf. It is *not* an ornament, but a virile instrument.

IVOR GRIFFITH.

Argyria. The Pharmacology of Silver. By William R. Hill, M. D., and Donald M. Pillsburg, M. A., M. D. Williams & Wilkins, 1939. $2.50.

This monograph represents a type of scientific labor which seems to us eminently worth while. Although the authors do not report

any experiments of their own, they have collated and systematized the published results of hundreds of previous observations, both on man and the lower animals. How complete is this critical review of the literature is shown by the fact that they quote from 600 articles dealing with argyria. The book may be said to truly represent present-day knowledge concerning this bizarre disfigurement. In addition there is a table, which should be of interest to pharmacists, giving the names of ninety-four proprietary compounds of silver. Into what a mire of ridiculous redundancy has commercialism in pharmacy lured the physician!

The outstanding conclusions brought out in this monograph are: (1) The number of cases of argyria has been steadily increasing during the last thirty years. (2) The condition, while often causing great disfigurement, has no apparent injurious effect on the general health. (3) The chemistry of the discoloration is not definitely known but is probably a deposit of either silver oxide or elemental silver in the skin. (4) The treatment is unsatisfactory; while a method of removing the discoloration has been devised, it is so tedious and painful that it is rarely practicable, and is not always successful. (5) The long continued local use of silver compounds, for their antiseptic action, is a frequent cause of such disfigurement.

H. C. Wood.

Popular Science Talks. Volume XII. 240 pages. Price $1. Published by *American Journal of Pharmacy.*

This latest volume in the series of Popular Science Talks represents another group of lectures delivered to the general public by members of the faculty of the Philadelphia College of Pharmacy and Science. It is a worthy addition to the twelve preceding books, ten of which are still available.

The new Volume XII presents the following topics: "Blood and the Criminal" and "Building Castles of Health," by Louis Gershenfeld, Ph. M.; "Sea—Inside," by Ivor Griffith, D. Sc.; "Milestones in Chemistry," by Arthur Osol, Ph. D.; "Out of the Trash Can" and "Out of Another Trash Can," by Freeman P. Stroup, Ph. M.; "His-

tory and Romance of Digitalis" and "The Drugs of the Bible," by John E. Kramer, B. Sc.; "National and International Standards for Medicine," by E. Fullerton Cook, Ph. M.; "Elements of Flight," by Charles C. Pines, M. Sc.; "Streamlines," by George Rosengarten, Ph. D.; "The Age of Obesity," by J. W. E. Harrisson, Ph. M.

Glass Cleaner

A paste for cleaning and polishing windows, mirrors, and similar glass products can be made, according to a report from abroad, from the following ingredients:

Curd soap	10 parts
Warm water	25 parts
Glycerin	15 parts
Alcohol	20 parts
Ammonia	sufficient
Precipitated chalk	50 parts
Kieselguhr	30 parts
Kaolin	20 parts

Dissolve the soap in the mixed liquids, add enough ammonia until solution is complete. The solution is then worked up with the previously mixed dry ingredients to form a paste. This is allowed to stand for a day or two, then is kneaded before being placed in suitable containers.

The addition of glycerin not only serves to maintain the essential moisture content of the paste, but lends a definite cleansing action of its own to the product.